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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,011	06/19/2006	Beatrice Schaack	284025US0XPCT	8486

22850 7590 12/16/2009

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,011	SCHAACK ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-21,24,25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-15,17-21,24,25 and 27-28* is/are rejected.

7)☒ Claim(s) *6,8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/09 has been entered.

Election/Restrictions

Applicant elected SEQ ID NO: 26 in claim 2 (beta subunit (SEQ ID NO: 90) in claim 1) with traverse in the response filed on 10/24/07. The office action mailed on 1/10/08 searched and examined SEQ ID NO: 26 in claim 2 and claim 1 with respect to SEQ ID NO: 90, but did not search and examined the other sequences in claims 1, 2, 6 and 8. The office action mailed on 10/10/08 included claims 6 (SEQ ID NO: 67) and 8 (SEQ ID NO: 83 and 86) in the examination.

In view of the prosecution history, claim 1a), b), (d) with respect to a) and b)), claim 2a),b), SEQ ID NOs: 27-40 and (d) with respect to a) and b)), 28a), b) and (d) with

respect to a) and b)), and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/24/07.

There is more than one nucleotide sequence recited in the instant claims. The Office decision to rescind the 1996 waiver (for examining up to 10 dependent and distinct nucleotide sequences) is based upon the increasing computational, search and examination burden required for the consideration of nucleic acids sequences, and complexity of claims drawn to such, compared to the time of the 1996 waiver. See http://www.uspto.gov/web/patents/patog/week13/OG/TOC.htm#ref14.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 23.

Claim Objections

Claim 27 is objected to because of the following informalities: subunit appears to be misspelled on line 4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 27 appears not to be supported by the as-filed specification. Applicant has not pointed out where the claim is supported, nor does there appear to be a written description of the claim limitation 'control cell' in the application as filed. See MPEP § 2163.06. The amendment filed on 7/10/08 did not provide support for what part of the disclosure supports claim 27. The examiner searched the specification and could not find support of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 3, 4, 5, 7, 10, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova (US 20050245475). Khvorova et al. teaches a siRNA molecule that is 100% identical to nucleotides 1-19 of SEQ ID NO: 26. See SEQ ID NO: 118,703. Khvorova et al. teach identifying targets and description of targets that can be used for making siRNA (Tables 12-15, Tables 1-4 in provisional 60/502,050). The last two nucleotides (TT) at the end of SEQ ID NO: 26 are missing from SEQ ID NO: 118,703. However, Khvorova teaches siRNA having a 3'-overhang comprising 1 to 6 nucleotides, including a dTdT and dTdT is one of the most common dinucleotides added to siRNA molecule (paragraphs 0114, 0118, and 0266). Khvorova teach that method of making siRNA molecules are well known to one of ordinary skill in the art (paragraphs 0266). Khvorova teaches siRNA molecules comprising a 2'-modified nucleotide or a phosphorothioate (paragraph 0120). Khvorova et al. teach a cell comprising a siRNA molecule (paragraph 0109). Khvorova et al. also teach a vector comprising a siRNA molecule (paragraph 0284). Khvorova et al. teaches a composition comprising siRNA and a carrier (paragraph 0277).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. '475 enjoys priority to provisional application 60/502,050 filed on 12/01/03. If applicant filed a translation of said papers, the instant application would enjoy priority to 7/2/2003.

Claim 9 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Wyatt et al. (US 6,440,738, of record).

Claims 9 and 11 read on a single-stranded oligonucleotide having 21 ribonucleotides, wherein the oligonucleotide is complementary to a fragment of a transcript a beta subunit included between positions 80-100, 116-137, 164-208, 369-389, 400-420, 527-592, 613-643 from the ATG codon with respect to SEQ ID NO: 90.

Wyatt discloses antisense oligonucleotides targeted to fragments of the beta-subunit of casein kinase 2 that is represented by SEQ ID NO: 3 (that corresponds to SEQ ID NO: 90). The antisense oligonucleotides that can be DNA or RNA and 8-50 nucleotides in length (columns 7 and 115). "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." See Merck & Co. v Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Thus, Wyatt teaches the claimed product.

Applicant's arguments filed 7/10/08 have been fully considered but they are not persuasive. In response to applicant's argument that Wyatt discloses an antisense

oligonucleotide that is a gapmer having 10 deoxynucleotides unlike the oligonucleotide of claim 9 and 11 composes of 17-21 ribonucleic acid flanked on the 3' end with 2 ribonucleotides reading on an antisense oligonucleotide having 21 ribonucleotides. Wyatt teaches that the antisense oligonucleotides can be DNA or RNA (column 7), thus Wyatt teaches antisense oligonucleotides having 21 ribonucleotides. "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned." "They are part of the literature of the art, relevant for all they contain." See In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 3, 4, 5, 7, 9, 10, 11, 15, 17, 18, 19, 20, 21, 24, 25, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt (US 6,440,738, of record) taken with Tuschl et al. (Tucshl1, US 20020086356) and Tuschl et al. (Tuschl2, siRNA user guide, 2001). SEQ ID NO: 3 of Wyatt corresponds to SEQ ID NO: 90 in the present application and Wyatt provides motivation for inhibiting its expression using an oligonucleotide (abstract and columns 1-3 and 115-116). Wyatt teaches an oligonucleotide sequence comprising α subunit, α' subunit, and the β subunit of CK2 protein kinase. Wyatt also teaches that penetration enhancer to help the efficiency of an oligonucleotide and pharmaceutical compositions comprising an oligonucleotide were known to one of ordinary skill in the art were known (columns 24-27). Wyatt further teaches that the composition can be combined with either a chemotherapeutic or anti-viral agent (columns 27-28). However, Wyatt does not specifically teach double stranded oligonucleotide having a sense strand that is a fragment of a transcript of beta subunit CK2 protein kinase with reference to SEQ ID NO: 90.

However, at the time the invention was made, it was well known at the time of filing of the instant application that siRNAs were extremely useful for "knocking down" gene expression by RNA interference (RNAi). Tuschl 1 and Tuschl2 teach that RNA interference, mediated by double-stranded small interfering RNAs (siRNAs), was very well-recognized as a very useful tool for studying gene function once the sequence of a gene is known, that RNAi was accessible to one of ordinary skill in the art, and that RNAi is now routine in laboratories. Tuschl1 teaches that siRNA duplexes provide a new tool for studying gene function in mammalian. Tuschl1 reports their systematic analysis of length, overhangs, and sequence determinants of siRNA function. Tuschl2 provides guidelines for designing efficient siRNAs for inhibiting target gene expression. Search for a sequence AA(N19)TT or AA(N21) with around 50% G/C content in the targeted sequence and compare the selected siRNA nucleotide sequence against public nucleotide sequence databases to ensure that only the desired gene will be targeted.

It would have been obvious to one of skill in the art at the time of filing of the instant application to make siRNAs to inhibit CK2 protein expression. Wyatt teaches that the CK2 protein kinase mRNA sequence was known and studies in which the gene expression had been eliminated had already been done. Thus, the teaching indicates that further research on CK2 protein kinase by one of ordinary skill in the art was warranted and that the kinase may be a good target gene for therapeutics. Because both Tuschl1 and Tuschl2 teach the ubiquitous use within the scientific community of siRNAs for interfering with gene expression, one of ordinary skill in the art would

immediately recognize siRNAs as an easy and routine way to inhibit CK2 protein gene expression for *in vitro* studies of the gene. Furthermore, Tuschl1 presents siRNAs as potential gene-specific therapeutics. One of ordinary skill in the art would recognize that siRNAs to CK2 protein kinase could serve as a therapeutic in light of the teachings of Tuschl1. Tuschl1 and Tuschl2 also make it clear that production of any siRNA sequence, including the instantly claimed double-stranded oligonucleotide, would be a matter of routine experimentation and optimization, as Tuschl2 set forth siRNA design guidelines. "The Board noted that the problem facing those in the art was to isolate a specific nucleic acid, and there were a limited number of methods available to do so." "The Board concluded that the skilled artisan would have had reason to try these methods with the reasonable expectation that at least one would be successful." "Thus, isolating the specific nucleic acid molecule claimed was "the product not of innovation but of ordinary skill and common sense."" See Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007). Tuschl2 teaches targeting a sequence beginning at 50 to 100 nt downstream of the start codon which for example would lead one of ordinary skill in the art to positions 80-100 with reference to SEQ ID NO: 90 of the present application. Three nucleotide sequences begin with AA in this region leading to a finite number of targets to design siRNA. Thus, the instant claims would have been obvious to one skilled in the art at the time of filing of the instant application. One of ordinary skill in the art would have been motivated to combine the teaching to study the inhibition of CK2 protein kinase in a cell. "The combination of familiar elements according to known

methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wyatt, Tuschl1, and Tuschl2, namely to produce a composition comprising the siRNA. One of ordinary skill in the art would have been motivated to combine the teaching to deliver the double-stranded oligonucleotide.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wyatt, Tuschl1, and Tuschl2, namely to produce a composition comprising the siRNA and at least one antiviral agent or anticancer agent. One of ordinary skill in the art would have been motivated to combine the teaching to study the effect of both products in a eukaryotic cell culture.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wyatt, Tuschl1, and Tuschl2, namely to produce a composition comprising the siRNA and at least one substance that allows targeting into cells. One of ordinary skill in the art would have been motivated to combine the teaching to study whether or not the substance improves delivery of the siRNA in a eukaryotic cell culture.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 12-14 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt, Tuschl1 and Tuschl2 as applied to claims 1, 2, 3, 4, 5, 7, 9, 10, 11, 15, 17, 18, 19, 20, 21, 24, 25, and 28 above, and further in view of Fosnaugh et al. (US 2003/014732, of record).

Wyatt, Tuschl1 and Tuschl2 do not specifically teach an expression vector comprising the double-stranded oligonucleotide.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs. In example 3, Fosnaugh et al. teach production of pools of siRNAs. Fosnaugh et al. is considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wyatt, Tuschl1, Tuschl2, in

further view of Fosnaugh, namely to produce the expression vector. One of ordinary skill in the art would have been motivated to combine the teaching to deliver the double-stranded oligonucleotide.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wyatt, Tuschl1, Tuschl2, in further view of Fosnaugh, namely to produce the composition comprising a mixture of at least one oligonucleotide specific for an α subunit, at least one oligonucleotide specific for the α' subunit, and at least one oligonucleotide specific for the β subunit of CK2 protein kinase. One of ordinary skill in the art would have been motivated to combine the teaching to study the inhibition of CK2 protein kinase in cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

Claims 6 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-

0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635